Polymeric Drugs & Drug Delivery Systems

R.M. Ottenbrite and S.W. Kim, eds.
Technomics Publishing Company, Inc., Lancaster, PA
Library of Congress Catalog Card No. 00-109967
ISBN No. 1-56676-956-6 2001

CHAPTER 21

Self-Etching, Polymerization-Initiating Primers for Dental Adhesion

CHETAN A. KHATRI[1]
JOSEPH M. ANTONUCCI[1]
GARY E. SCHUMACHER[2]

INTRODUCTION

DENTIN is a complex heterogeneous substrate consisting mainly of water, collagen, and hydroxyapatite that varies in microstructure and composition between its enamel and pulpal boundaries [1]. Because of this complexity, the bonding of polymerizable resin-based materials such as dental composites to this substrate is not as straightforward as bonding to enamel that requires simple acid etching and, as a consequence, requires more sophisticated types of surface treatments. Effective adhesive bonds between dentin and dental restorative materials have been achieved by the sequential application of a series of solutions to the dentin surface. For example, application of a three-part adhesive system consists of (1) a conditioner or etchant such as aqueous nitric or phosphoric acid, (2) a primer such as *N*-phenylglycine (NPG) in acetone, and (3) an acetone solution of a multifunctional surface active monomer, such as 1,4-di[2′-(2′-methyl-2′-propenate)ethyl]phthalate-2,5-dicarboxylic acid (*para*-PMDM), the product from the reaction of pyromellitic dianhydride and 2-hydroxyethyl methacrylate [2]. The crystalline para product is separated by filtration from the meta isomer byproduct. Shown on Figure 1 is the synthetic scheme for the preparation of *para*-PMDM.

[1]Polymers Division, National Institute of Standards and Technology, Gaithersburg, MD 20899-8545, USA.
[2]American Dental Association Health Foundation, Paffenbarger Research Center, NIST, Gaithersburg, MD 20899-8545, USA.

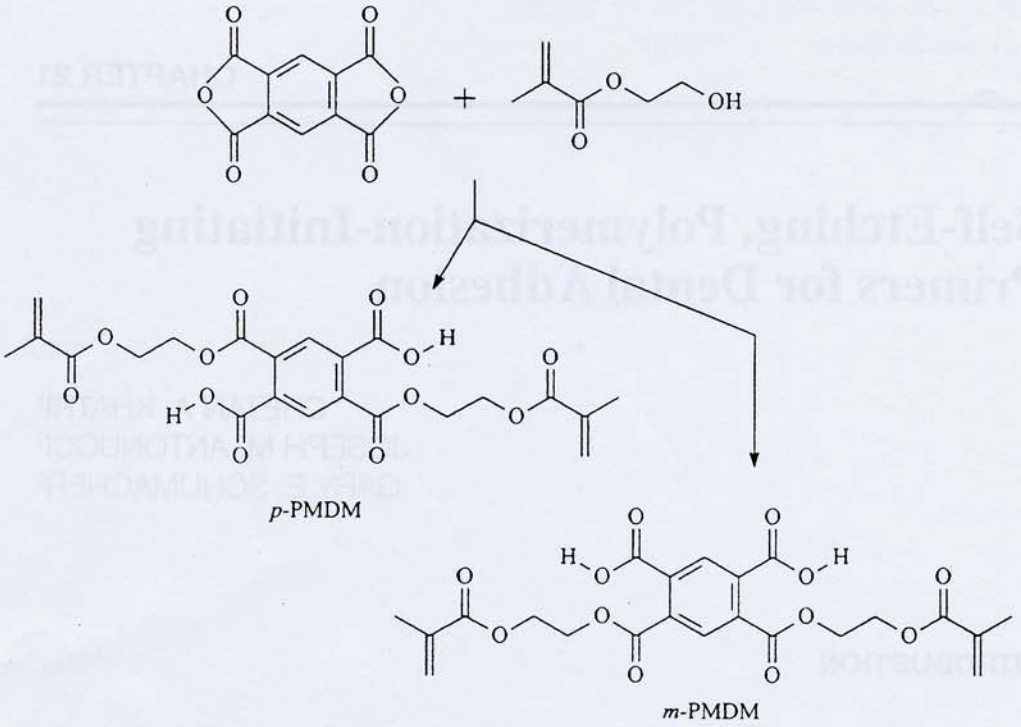


Figure 1 Synthesis of 1,4-di[2′-(2′-methyl-2′-propenate)ethyl]phthalate-2,5-dicarboxylic acid (*p*-PMDM).

In the usual multistep adhesive protocol the role of nitric acid or similar strong acid is to act as an etchant or conditioning agent to cleanse the substrate by removing the smear layer from cut and ground dentin and also to create a microporous surface with open tubules. A surface-active primer such as NPG then diffuses into the conditioned dentinal surface where it stabilizes the demineralized collagen against collapse and facilitates diffusion of *para*-PMDM and by an acid-base reaction complexes with the carboxylic acid monomer. Previous studies indicate that such complexes are unstable and decompose into radicals, which are capable of initiating interfacial copolymerization of this carboxylic acid adhesive monomer with a bonding resin or with the resin phase of the composite as shown in Figure 2 [3,4]. NPG can act as an effective photoreductant for photosensitive oxidants such as camphorquinone to generate initiating radicals via an exciplex [3].

The use of strongly acidic conditioners such as nitric or phosphoric acid may excessively demineralize dentin and create a highly decalcified collagenous zone that is not optimal for bonding because it may not be completely infiltrated with the primer and adhesive resin. A less-aggressive decalcifying agent is the chelating acid ethylenediamine tetraacetic acid (EDTA), which is used in the form of a soluble salt because of its poor solubility. It would be desirable to have a soluble analog of EDTA that can

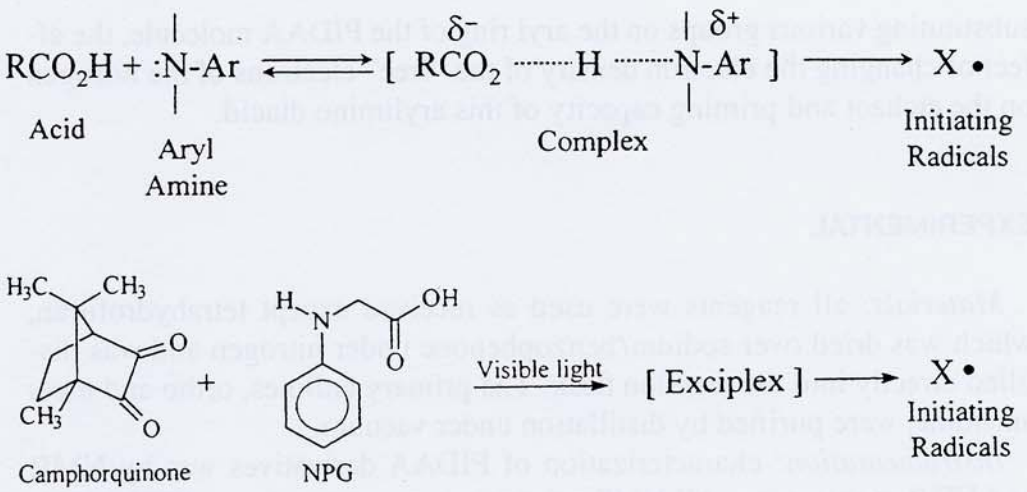


Figure 2 (a) Radical formation through complex formation between a carboxylic acid and an aryl amine such as NPG. (b) Photogeneration of initiating radicals via an exciplex formed by camphorquinone and NPG.

also act as a primer and, thereby, reduce the usual three-step bonding protocol to two steps by combining etchant and primer functions in one compound. In previous studies it was shown that *N*-phenyliminodiacetic acid (PIDAA) has these properties and also can self-initiate polymerization of several acrylic monomers [3,4]. PIDAA has a structure intermediate between NPG and EDTA as shown in Figure 3, and this unique structure enables it to function as a self-etching primer with the ability to initiate and co-initiate the polymerization of dental monomers.

Due to its aromatic iminodiacetic acid structure, PIDAA is not only more acidic than NPG but is also a more efficient chelator for Ca^{+2}. Thus it can effectively serve both as an etchant and as a primer like NPG because of its arylamine structure. To gain further insight into the mechanism of the spontaneous polymerization of acrylics caused by PIDAA, several derivatives of PIDDA with electron-withdrawing or -donating aromatic ring substituents were prepared. The rationale for this study was to ascertain, by

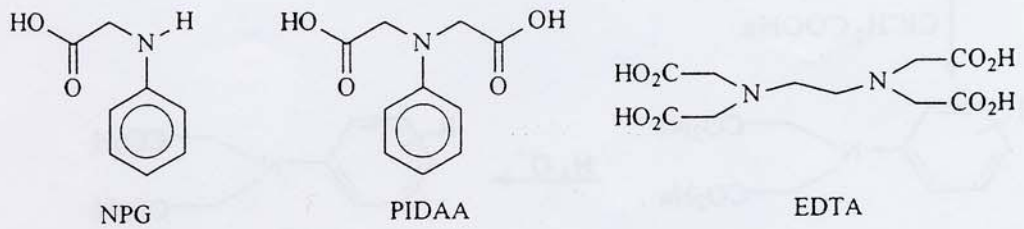


Figure 3 Chemical structures of *N*-phenylglycine, *N*-phenyliminodiacetic acid, and ethylenediaminetetraacetic acid.

substituting various groups on the aryl ring of the PIDAA molecule, the effect of changing the electron density of the "free" electrons of the nitrogen on the etchant and priming capacity of this arylimino diacid.

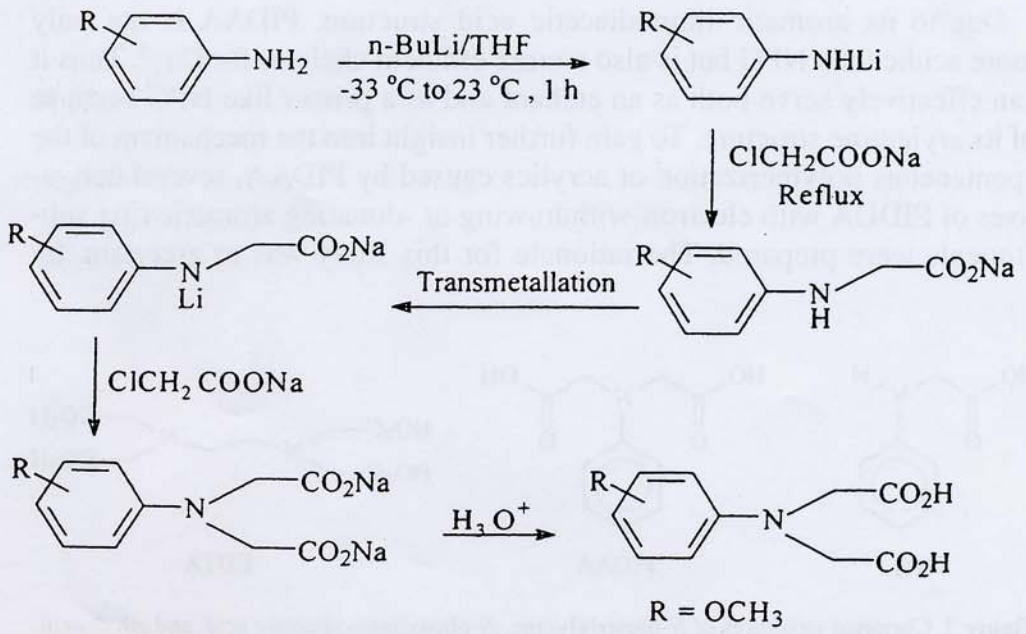
EXPERIMENTAL

Materials: all reagents were used as received except tetrahydrofuran, which was dried over sodium/benzophenone under nitrogen and was distilled directly into the reaction flask. The primary anilines, ortho and meta anisidine, were purified by distillation under vacuum.

Instrumentation: characterization of PIDAA derivatives was by NMR and FTIR spectroscop. All NMR spectra were measured on a JEOL GSX-270 instrument using DMSO-*d6* as the solvent and tetramethylsilane (TMS) as a reference at 0.00 ppm. The standard uncertainties are 0.02 ppm for ^{1}H-NMR and 0.05 ppm for ^{13}C-NMR, respectively. FTIR spectra of solids were recorded in KBr pellets on a Nicolet Magna 550 FTIR.

SYNTHETIC PROCEDURE I [5]

Scheme-1 was used for the synthesis of 3- and 4-methoxy-substituted PIDAA derivatives. Under an inert atmosphere to an oven dried flask was added 4.72 g (0.0383 mol) of the appropriate anisidine. About 50 mL of



Scheme 1.

THF was then transferred by a vacuum transfer technique. After the solution was stirred at room temperature for 5 min and brought to − 30°C, 24.7 mL (0.0396 mol) of 1.6 mol/L *n*-butyl lithium in hexane was added with stirring. The solution was stirred at this temperature for 1 h and at 23°C for an additional 90 min; then 15.6 g (0.1339 mol) of sodium chloroacetate was added, and the mixture was refluxed for 24 h. The mixture was brought to room temperature and the solvent removed under *vacuo*. The residue was dissolved in 50 mL of water and extracted three times with 30 mL of dichloromethane. The aqueous layer was then acidified with 12 M. HCl until precipitation was observed. The flask was then warmed on water bath until a clear solution was obtained and then stored at 5°C overnight. Almost colorless crystals were obtained by filtration of the mixture. The product was dried under high vacuum and then stored in a tightly sealed vial in refrigerator. Yields were between 55% and 60% based on *n*-butyl lithium.

For 4-methoxy-PIDAA, ^{1}H-NMR showed peaks at (12.44 (broad singlet), 6.77 (doublet), 6.45 (doublet), 4.05 (singlet), and 3.64 (singlet)) ppm. ^{13}C-NMR showed peaks at 173.25, 151.88, 142.71, 115.15, 113.33, 55.86, and 53.97 ppm. For 3-methoxy-PIDAA, ^{1}H-NMR showed peaks at 12.68 (broad singlet), 7.06 (triplet), 6.28 (doublet), 6.12 (doublet), 6.00 (doublet), 4.07 (singlet), and 3.67 (singlet) ppm. ^{13}C NMR showed peaks at 172.92, 160.83, 149.73, 130.32, 105.18, 102.45, 98.73, 55.34, and 53.66 ppm.

SYNTHETIC PROCEDURE II [6,7]

The following procedure [6] was used to synthesize 1,4-phenylenediiminotetracetic acid. 1,4-phenylenediamine (10.8 g, 0.1 mol), chloroacetic acid (37.8 g, 0.4 mol), sodium hydroxide (32.0 g, 0.8 mol), and potassium iodide (5.0 g, 0.03 mol) in 500 mL of water was refluxed for 2 h and then 40 mL of conc. HCl was added. The reaction mixture was cooled in an ice/water mixture. Slightly pink colored crystals separated out, which were vacuum filtered and dried in a vacuum oven; yield 21.5 g. For 1,4-phenylenediaminetetraacetic acid, ^{1}H-NMR showed peaks at 11.99 (broad singlet), 6.42 (singlet), and 4.01 (singlet) ppm. ^{13}C-NMR showed peaks at 173.56, 140.38, 113.49, and 54.06 ppm.

The 3- and 4-methoxy-substituted PIDAA derivatives were also synthesized by following the above procedure. The ^{1}H- and ^{13}C-NMR spectra were similar to those listed under synthetic procedure I. The 2-, 3-, and 4-carboxy-substituted PIDAA derivatives and 3-acetyl PIDAA derivatives also were synthesized by synthetic procedure II as described below [7].

To 10.3 g, 0.075 mol aminobenzoic acid neutralized with 5 mol/L sodium hydroxide (or to 3-acetyl aniline in 250 mL of water), was added sodium chloroacetate (26.2 g, 0.225 mol). The solution was refluxed, and the pH was maintained between 10 and 12 by the addition of 5 M aqueous sodium hydroxide solution. After the pH ceased to fall, the solution was refluxed for an additional 1 h and then cooled and acidified with 0.5 mol/L HCl. The crystals were vacuum filtered and dried under high vacuum. The product was recrystallized from an acetone/water mixture. The yield of these aryliminodiacetic acids reaction varied from 3.1 g to 5.3 g.

- For 4-carboxy-PIDAA, the ^{1}H-NMR showed peaks at 12.55 (broad singlet), 7.71 (doublet), 6.53 (doublet), and 4.16 (singlet) ppm. ^{13}C-NMR showed peaks at 172.13, 167.83, 151.93, 131.46, 118.98, 111.43, and 53.29 ppm.
- For 3-carboxy-PIDAA, the ^{1}H-NMR showed peaks at 13.31 (broad singlet), 7.24 (singlet), 7.10 (multiplet), 6.77 (singlet), 6.69 (singlet), and 4.05 (singlet) ppm. ^{13}C-NMR showed peaks at 173.76, 168.33, 147.94, 132.04, 129.69, 117.90, 115.82, 112.14, and 55.91 ppm.
- For 2-carboxy-PIDAA, the ^{1}H-NMR showed peaks at 13.23 (broad singlet), 7.83 (doublet), 7.50 (multiplet), 7.39 (doublet), 7.17 (t), and 3.98 (singlet) ppm. ^{13}C-NMR showed peaks at 171.52, 167.92, 149.69, 135.51, 131.71, 125.18, 124.61, 127.79, and 55.86 ppm.

When 2-anisidine, *p*-acetylaniline, 1,2-phenylenediamine, and 2-trifluromethylaniline were used, the above procedure gave only monosubstituted or *N*-phenylglycine derivatives.

SEM EVALUATION OF DENTIN TREATED WITH THE PIDAA DERIVATIVES

A scanning electron microscope, SEM (JEOL JSM-5300, JEOL USA, Inc., Peabody MA) was used to examine the morphology of dentin surfaces treated with solutions of various PIDAA derivatives at concentrations of 0.1 and 0.3 mol/L. The surfaces of dentin discs were treated for 60 s, placed in a vacuum desiccator (2.7 kPa) at room temperature for 24 h, gold sputter coated, and examined by SEM.

POLYMERIZATION OF 2-HYDROXYETHYL METHACRYLATE (HEMA) AND METHYL METHACRYLATE (MMA)

To 2 g of HEMA or MMA in a vial was added a mass fraction of 0.37 PIDAA derivative. The vial is shaken to dissolve the PIDAA derivative and left standing at room temperature. Only the 3- and 4-methoxy-substituted PIDAA derivatives dissolved in HEMA and MMA. For other derivatives,

a solution in acetone/water was used. Polymerization was noted visually by tilting the vial and observing the increase in viscosity until the solution gelled completely.

RESULTS AND DISCUSSION

The ability of mineral acids such as dilute nitric and phosphoric acid to etch the dentinal surface and remove the smear layer is well known. *N*-Phenyliminodiacetic acid (PIDAA) is more acidic ($pK_1 = 2.5$) [8] than *N*-phenylglycine ($pK_a = 4.4–5.4$) [9] and also can chelate metal ions, including Ca^{+2}. Therefore, PIDAA has additional potential for modifying the smear layer created by cutting and grinding dentin in dental procedures. As expected from the structural similarity to NPG, PIDAA also has been shown to stabilize demineralized collagen and facilitate the diffusion of adhesive monomers into decalcified dentin. As in the case of NPG, PIDAA is capable of activating monomers by acid–amine complexation for radical polymerization. This self-initiation radical mechanism could either be due to intermolecular complex formation between the tertiary aryl amine and the carboxy group of the monomer or by the formation of an intramolecular zwitterionic dipolar species [4,10,11]. These potential pathways are shown in the Figure 4.

In either the intramolecular or intermolecular pathway, the ability to form such a complex could be enhanced by increasing the basicity or electron

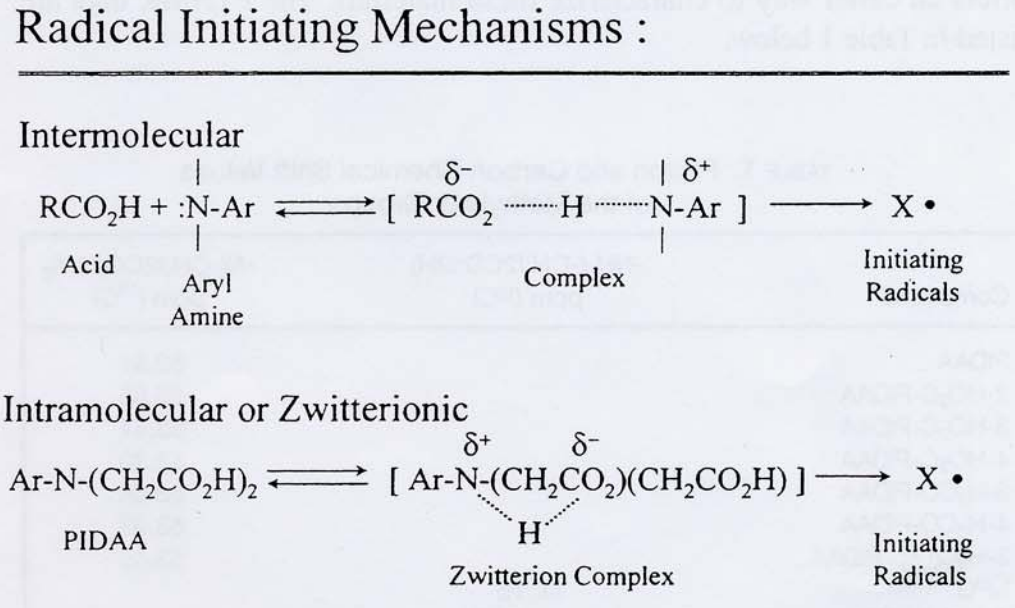
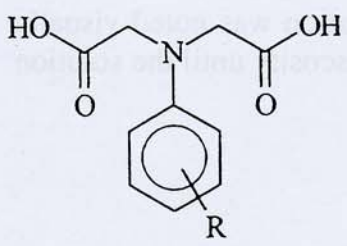


Figure 4 Plausible self-initiation mechanism of acrylic monomers with PIDAA.



R = 2-CO_2H, 3-CO_2H, 4-CO_2H
3-OCH_3, 4-OCH_3, 3-$COCH_3$

1,4-phenylenediamine tetraacetic acid

Figure 5 Chemical structures of PIDAA derivatives and 1,4-phenylenediaminetetracetic acid.

density of the nitrogen. One way to achieve this would be to substitute electron-donating groups on the aromatic ring. Accordingly, we synthesized several derivatives of PIDAA possessing either electron-withdrawing or electron-donating groups on the aromatic ring. Their structures are shown in Figure 5.

These derivatives are soluble in an acetone/water mixture with their pK_1 values similar to that of PIDAA. The phenylene analogs are similar to EDTA except that the two nitrogens are bridged by aromatic rings. These derivatives are soluble in acetone/water. They were characterized by measuring their ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra and Fourier transform infrared (FTIR) spectra. All the PIDAA derivatives showed a peak near 53 ppm for the methylene carbons in carbon NMR spectra. The methylene carbon resonance appears around 44 ppm in the NPG derivative. Thus offers an easier way to characterize these materials. The FTNMR data are listed in Table 1 below.

TABLE 1. Proton and Carbon Chemical Shift Values of the Methylene Groups.

Compound	-NH-(-CH;I2CO;I2H) ppm (^{13}C)	-N(-CH;I2CO;I2H)$_2$ ppm (^{13}C)
PIDAA		52.91
2-HO_2C-PIDAA		55.86
3-HO_2C-PIDAA		53.41
4-HO_2C-PIDAA		53.30
3-H_3CO-PIDAA		53.66
4-H_3CO-PIDAA		53.97
3-$H_3C(O)C$-PIDAA		53.45
NPG	44.15	
2-H_3CO-NPG	44.62	

FTIR studies on 2- and 4-carboxy-substituted NPG derivatives and for 2- and 4-carboxy-substituted PIDAA derivatives showed an absorbance at 3,460 cm^{-1} for NPG derivative, which was absent in the PIDAA derivatives. Figure 6 and 7 shows these differences in 2- and 4-carboxy NPG and in 2- and 4-carboxy PIDAA.

The SEM micrographs of dentin surfaces treated with an aqueous acetone solution (mass ratio 1 : 1) containing 0.3 mol/L 3-methoxy PIDAA indicated significant removal of the smear layer by 3-methoxy PIDAA (3 MeOPID), similar to that achieved with PIDAA (Figure 8). Similar observations were made with the other PIDAA derivatives.

A preliminary study comparing the polymerization-initiating potential of the various PIDAA derivatives suggested the PIDAA derivatives with electron-donating groups were able to polymerize HEMA and MMA more rapidly compared with PIDAA. PIDAA alone was able to initiate the polymerization of these monomers faster compared with PIDAA derivatives with electron-withdrawing substituents. It is known that aliphatic amino acids

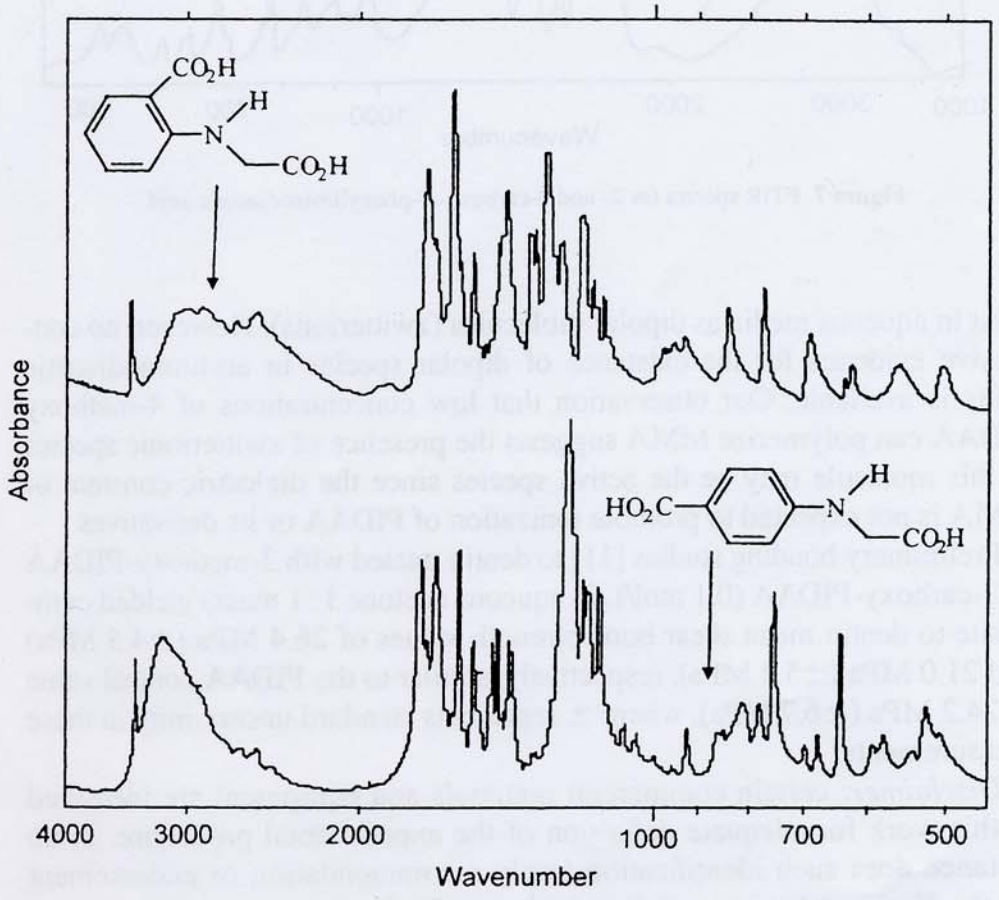


Figure 6 FTIR spectra for 2- and 4-carboxy-*N*-phenylglycine.

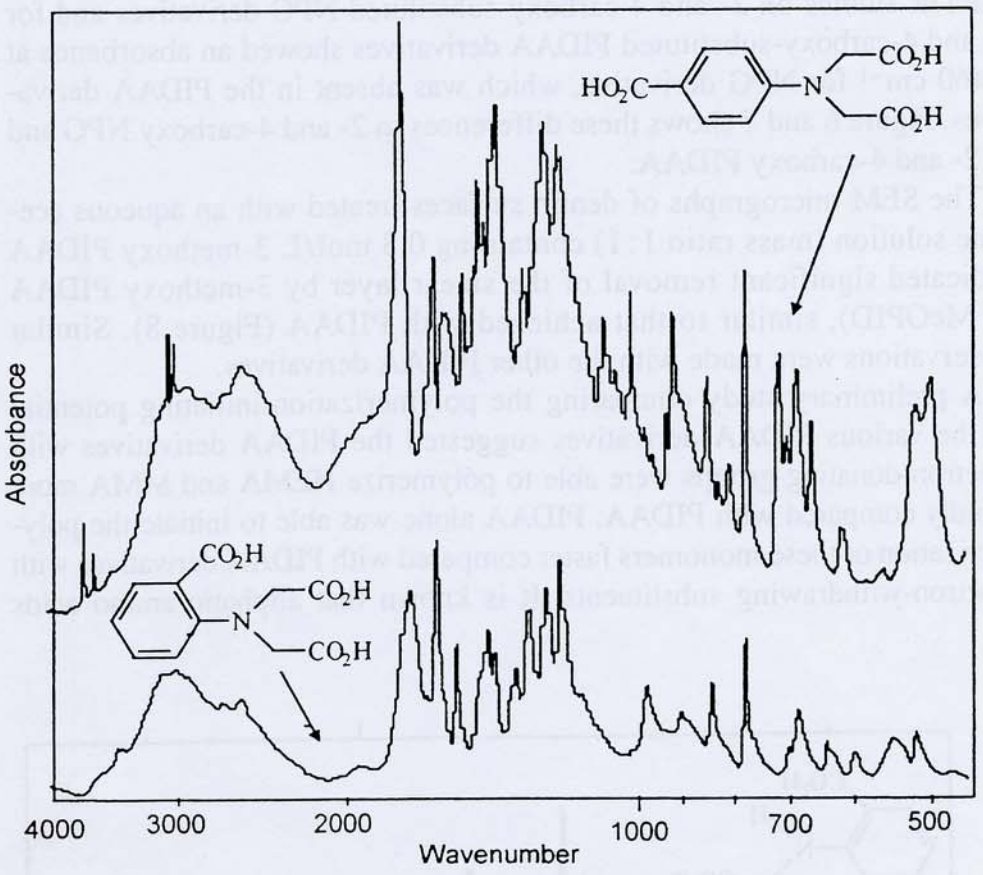
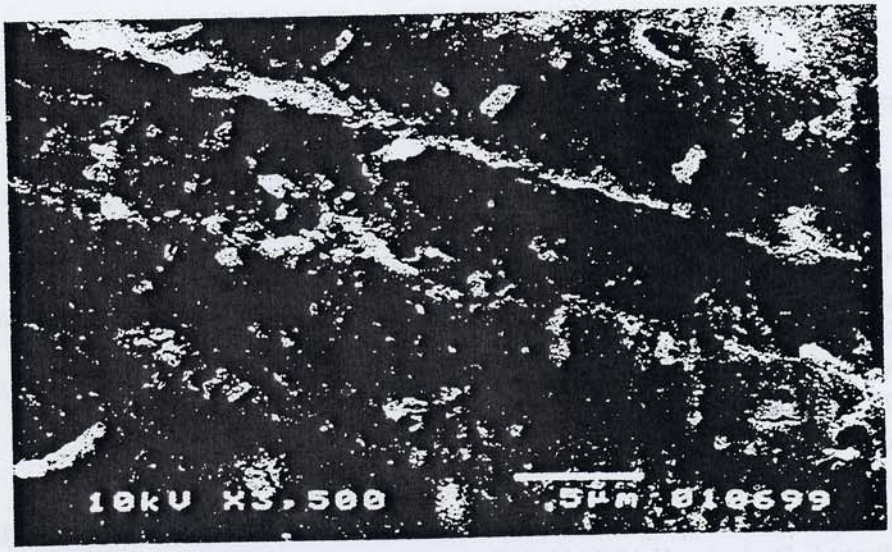


Figure 7 FTIR spectra for 2- and 4-carboxy-*N*-phenyliminodiacetic acid.

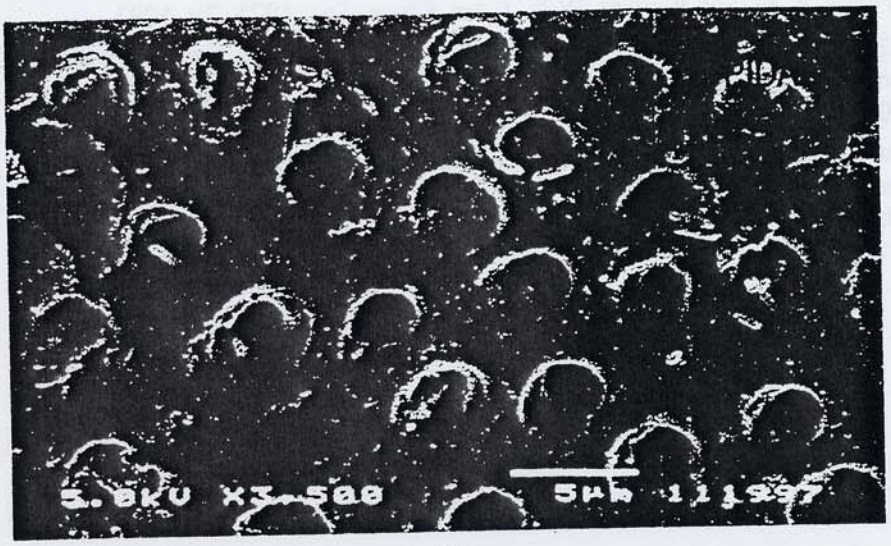
exist in aqueous media as dipolar molecules (zwitterions). However, no conclusive evidence for the existence of dipolar species in aryliminodiacetic acids is available. Our observation that low concentrations of 4-methoxy PIDAA can polymerize MMA suggests the presence of zwitterionic species in this molecule may be the active species since the dielectric constant of MMA is not expected to promote ionization of PIDAA or its derivatives.

Preliminary bonding studies [11] to dentin treated with 3-methoxy-PIDAA or 2-carboxy-PIDAA (0.1 mol/L in aqueous acetone 1 : 1 mass) yielded composite to dentin mean shear bond strength values of 26.4 MPa (±4.5 MPa) and 21.0 MPa (±5.4 MPa), respectively, similar to the PIDAA control value of 24.2 MPa (±6.7 MPa), where ± represents standard uncertainity in these measurements.

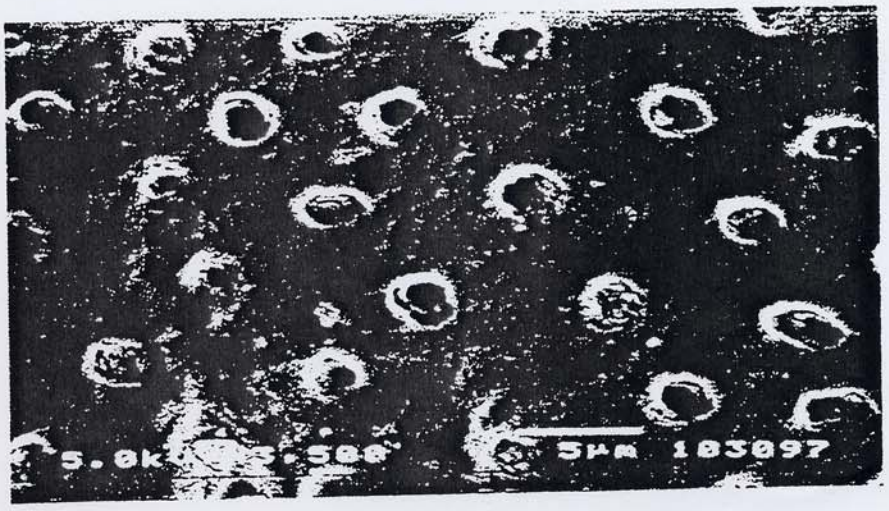
Disclaimer: certain commercial materials and equipment are identified in this work for adequate definition of the experimental procedure. In no instance does such identification imply recommendation or endorsement by the National Institute of Standards and Technology or that the equipment identified is necessarily the best available for the purpose used.



(a)



(b)



(c)

Figure 8 SEM Photomicrographs of dentin with (a) smear layer untreated. (b) treated with PIDAA. and (c) treated with 3-methoxy-PIDAA (3 MeOPID).

REFERENCES

1. Nakabayashi, N. and Pashley, D.H. *Hybridization of Dental Hard Tissues* 1998, Chapter 2, Quintessence Publishing Co., Ltd., Tokyo, Japan.
2. Bowen, R.L., Cobb, E.N., and Rapson, J.E. *Int. Dent. J.* 1987, 37, 158.
3. Code, J.E., Antonucci, J.M., Bennett, P.S., and Schumacher, G.E. *Dent. Mater.* 1997, 13, 252.
4. Schumacher, G.E., Antonucci, J.M., Bennett, P.S., and Code, J.E. *J. Dent. Res.* 1997, 76, 602.
5. Lin, S.T. and Huang, R.J. *Synthesis* 1989, 584.
6. Cox, J.R. and Smith, B.D *J. Org. Chem.* 1964, 29, 488.

7a. Schwarzenbach, V.G., Willi, A., and Bach, R.O. *Helv. Chim. Acta.* 1947, 30, 1303; **7b** Pettit L.D., Irving H.M.N.H. *J. Chem. Soc.* 1964, 5336.

8. Tichane, R.M. and Bennett, W.E. *J. Am. Chem. Soc.* 1975, 79, 1293.
9. Bryson, A., Davies, N.R., and Serjeant, E.P. *J. Am. Chem. Soc.* 1963, 85, 1933.
10. Farhani, M., Antonucci, J.M., Phinney, C.S., and Karam, L.R. *J. Appl. Polym. Sci.* 1997, 65, 561.
11. Antonucci, J.M., Khatri, C.A., Schumacher, G.E., Nikaido, T., and Code, J.E. *Proceedings of the 21st Annual Meeting of the Adhesion Society*, Savannah, GA., Feb. 22–25, 1998, 126–128.